REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully traversed. Pursuant to 37 C.F.R. § 1.21, attached as an appendix is a version with markings to show changes made to the specification and the claims.

Serotonin, dopamine, and norepinephrine are known to be important chemical messengers participating in the transmission of nerve impulses in the brain. These messengers are liberated at specific sites on pre-synaptic cells and received, to complete transmission of the impulse, at specific sites on post-synaptic cells. Their effect is then terminated by metabolism or by uptake into the pre-synaptic cells. Drugs capable of blocking the pre-synaptosomal uptake of either of these chemical messengers in the brain, are useful in alleviating disorders associated with decreased levels of these chemical messengers. For example, duloxetine and fluoxetine which are known serotonin reuptake inhibitors have been found to be useful in the treatment of depression, obesity, and obsessive-compulsive disease (U.S. Patent No. 5,532,244 to Wong, et al.). Also, U.S. Patent No. 5,444,070 to Moldt, et al., discloses the use of dopamine reuptake inhibitors in the treatment of depression, Parkinsonism, drug addiction and/or abuse, cocaine and/or amphetamine addiction and/or abuse. U.S. Patent No. 6,136,803 to Freedman, et al., also discloses synaptic norepinephrine or serotonin uptake inhibitors which are useful in treating depression in a patient. Furthermore, U.S. Patent No. 5,789,449 to Norden discloses the use of serotonin re-uptake inhibitors in treating psychiatric symptoms consisting of anger, rejection sensitivity, and lack of mental or physical energy. Also, U.S. Patent No. 4,902,710 to Foster, et al., discloses the use of serotonin and norepinephrine uptake inhibitors in suppressing the desire of humans to smoke or consume alcohol. Thus, there continues to remain a need to develop novel compounds which block reuptake of norephinephrine, dopamine, or serotonin.

Compounds which inhibit the reuptake of serotonin or norephinephrine, have also been used in combination therapy. For example, U.S. Patent No. 6,121,261 to Glatt, et al., discloses the use of selective serotonin reuptake inhibitors or norephinephrine uptake inhibitors, in combination with a neurokinin-1 receptor antagonist for treating attention deficit disorder in a patient.

Also, U.S. Patent No. 4,843,071 to Hohenwarter discloses the use of a norepinephrine re-uptake inhibitor and a norepinephrine precursor in the treatment of obesity, drug abuse, or narcolepsy in a patient. Furthermore, U.S. Patent No. 5,532,244 to Wong, et al., discloses the use of serotonin reuptake inhibitors in combination with a serotonin IA receptor antagonist, to increase the availability of serotonin, norepinephrine, and dopamine in the brain.

The treatment of a variety of neurological and psychiatric disorders is characterized by a number of side effects believed to be due to the compounds' inability to selectively block certain neurochemicals, and not others. ADHD, for example, is a disease affecting 3-6% of school age children and is also recognized in adults. Aside from hampering performance at school and at work, ADHD is a significant risk factor for the subsequent development of anxiety disorders, depression, conduct disorder, and drug abuse. Since current treatment regimes require psychostimulants and since a substantial number of patients (30%) are resistant to stimulants or cannot tolerate their side effects, there is a need for a new drug or class of drugs which treats ADHD and does not have resistance or side effect problems. In addition, methylphenidate, the current drug of choice for the treatment of ADHD, induces a number of side effects; these include anorexia, insomnia and jittery feelings, tics, as well as increased blood pressure, and heart rate secondary to the activation of the sympathetic nervous system. However, methylphenidate also has a high selectivity for the dopamine transporter protein over the norepinephrine transporter protein (DAT/NET Ki ratio of 0.1), which can lead to addiction liability and requires multiple doses per day for optimal efficacy. Thus, there continues to remain a need to develop novel compounds which block reuptake of norepbinephrine, dopamine, and serotonin with particular selectivity ratios.

U.S. Patent No. 3,947,456 discloses tetrahydroisoquinolines which are said to have utility as anti-depressants. U.S. Patent No. 3,666,763 describes the use of phenyl tetrahydroisoquinoline derivatives as antidepressants and antihypotensives. Canadian Patent Application No. 2,015,114 discloses the use of phenyl tetrahydroisoquinoline derivatives as antidepressants, which are apparently nonselective as to norepinephrine, serotonin, and dopamine uptake. UK Patent Application No. 2,271,566 discloses the use of phenyl tetrahydroisoquinoline derivatives as anti-HIV agents. W098/40358 discloses the use of phenyl tetrahydroisoquinoline derivatives to be useful in the treatment of disorders of glucose metabolic pathways. W097/36876 discloses the use of phenyl tetrahydroisoquinoline

derivatives as anticancer agents. W097/23458 describes 4-phenyl-substituted tetrahydroisoquinolines as NMDA receptor ligands useful for conditions associated with neuronal loss. Phenyl-substituted tetrahydroisoquinolines are also described in Mondeshka *et al* Il Farmaco 49:475-481 (1994).

Nomifensine®, which is a 4-phenyl-substituted tetrahydroisoquinoline derivative, is known to inhibit the neuronal uptake of dopamine and other catecholamines and has shown clinical efficacy for ADHD. However, long term administration of Nomifensine® results in fatal immune hemolytic anemia. Thus, there continues to remain a need to develop novel compounds which treat ADHD but do not have the serious side effects associated with Nomifensine® or the currently prescribed psychostimulants.

The present invention discloses novel aryl and heteroaryl substituted tetrahydroisoquinoline derivatives compounds which block reuptake of norephinephrine, dopamine, or serotonin, and are useful as alternatives to methylphenidate, and known psychostimulants, in the treatment of ADHD and other neurological and psychiatric disorders.

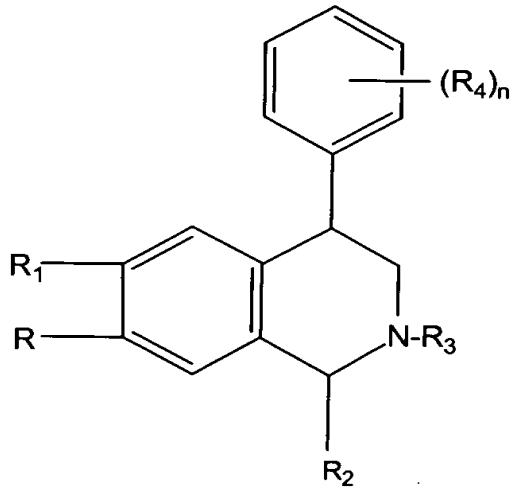
Applicants have discovered that the claimed compounds block reuptake of norephinephrine, dopamine, and serotonin with particular selectivity ratios (greater selectivity for the norepinephrine transporter (NET) protein than dopamine transporter (DAT) protein or serotonin transporter (SERT) protein (lower Ki for NET than for DAT and SERT)). It is postulated that the compounds would therefore be effective as an ADHD treatment with reduced addictive liability profiles. In particular, some of the compounds of the present invention are surprisingly and particularly selective for NET over the SERT protein, thus also affording compounds without the known side effect profiles of the selective serotonin reuptake inhibitor (SSRI) class of compounds.

The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 102(b) as anticipated by Tirelli, et. al., "Differential Effects of Direct and Indirect Dopamine Agonists on the Induction of Gnawing in C57B1/6J Mice", J. Pharm. & Exper. Therap. 273(1): 7-16 (1995)("Tirelli"), Salama, et. al., "Antigenic Determinants Responsible for the Reactions of Drug-Dependent Antibodies with Blood Cells," Brit. J. Haemotol. 78: 535-39 (1991)("Salama"), Swiss Patent Application Serial No. 538477 to F. Hoffmann-LaRoche ("Swiss Application"), or German Patent Application Serial No. 2,062,001 to F. Hoffmann-LaRoche ("German Application") is respectfully traversed.

Tirelli studies the differential effects of direct and indirect dopamine agonists on the induction of gnawing in C57BI/6J Mice. In carrying out this study, the effects of, *inter alia*, dichlofensine were examined.

Salama determines the antigenic combination sites of drug-dependent antibodies in patients with a drug-related immune haemolysis by assessing reactivity of 35 nomifensine-induced antibodies against human red blood cells in the presence of 11 closely related compounds, including diclofensine and 3 main metabolites. Figure 1 of Salama shows diclofensine (compound D) and its 3 main metabolites (compounds D1 to D3).

The Swiss and German Applications describe compounds of the following formula:



R is hydroxy or alkoxy;

R_1 is hydrogen, hydroxy, or alkoxy, where R and R_1 together can be methylenedioxy group;

R_2 is hydrogen or alkyl;

R_3 is alkyl, or aralkyl;

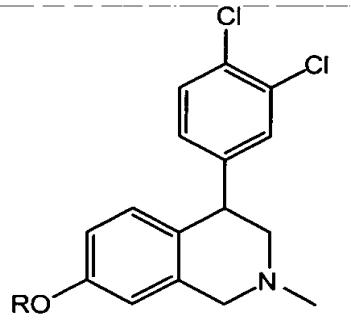
R_4 is halogen, nitro, or a mono- or di-substituted amino group; and

n is 1 or 2.

The specific compounds disclosed by the Swiss and German applications involve substitution of the pendant aryl ring with 3-chloro, 4-chloro, or 3,4-dichlorophenyl, while the 6-position and 7-position substituents are 6-methoxy, 7-methoxy, or 6,7-dimethoxyphenyl.

The accompanying Declaration of Bruce F. Molino under 37 C.F.R. § 1.132 ("Molino Declaration") is presented to demonstrate that compounds of the present application achieve a binding affinity for DAT to binding affinity for NET ratio of at least 2:1 and a binding affinity for SERT to binding affinity for NET ratio of at least 20:1, while dichlofensine and a metabolite of dichlofensine do not (Molino Declaration ¶4).

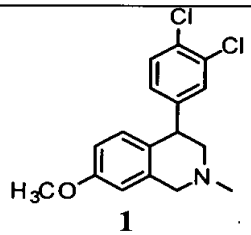
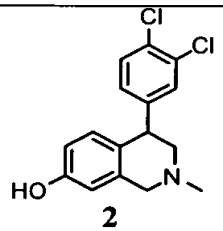
In particular, in addition to the compounds of the present invention (identified below as the PH-7032 compounds), the following compounds were tested:

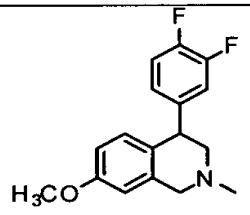
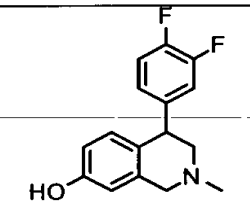
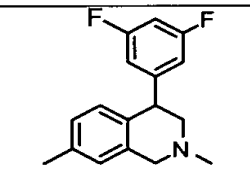
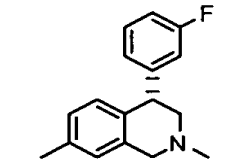
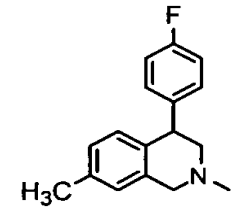
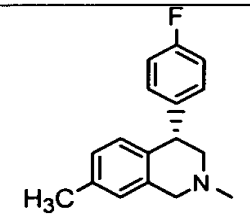


R=Me, dichlofensine, **1**
R=H, metabolite of dichlofensine, **2**

(Molino Declaration ¶5). These tests involved the binding assays described in paragraphs 6 and 7 of the Molino Declaration. The results of these binding assays for the various compounds tested are set forth in Tables 1 and 2 below.

Table 1

Compounds	NET, Ki nM	DAT, Ki nM	Selectivity DAT/NET
 **1** **racemate**	55	24	0.44
 **2** **racemate**	8	14	1.8

 PH-7032 compound Racemate	14	90	6.4
 PH-7032 compound Racemate	30	335	11.2
 PH-7032 compound Racemate	32	302	9.4
 PH-7032 compound (S)-(+)-enantiomer	12	94	7.8
 PH-7032 compound Racemate	15	76.5	5.1
 PH-7032 compound	7	36	5.1

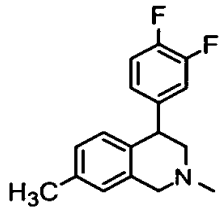
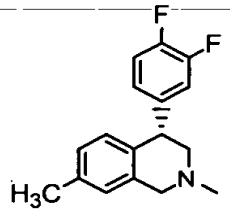
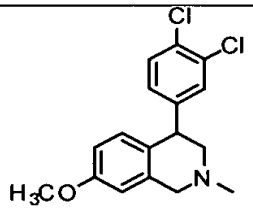
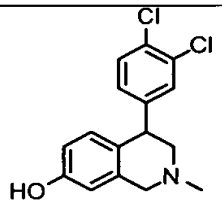
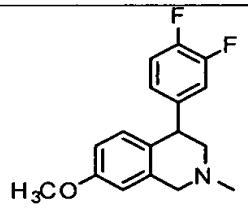
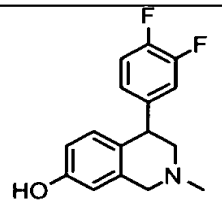
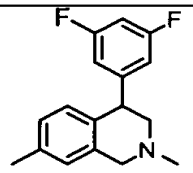
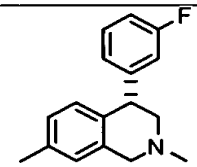
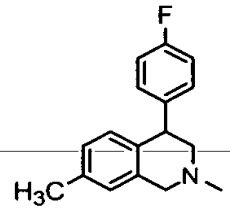
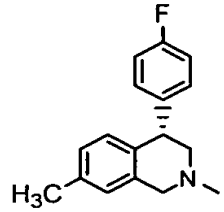
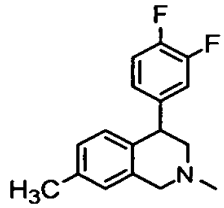
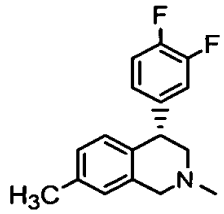
(S)-(+)-enantiomer			
 PH-7032 compound Racemate	25.5	180	7.0
 PH-7032 compound (S)-(+)-enantiomer	12.5	136	10.9

Table 2

Compounds	NET, Ki nM	SERT, Ki nM	Selectivity SERT/NET
 **1** **racemate**	55	285	5.2
 **2** **racemate**	8	13	1.6
 PH-7032 compound racemate	14	404	29
 PH-7032 compound racemate	30	867	29
 PH-7032 compound racemate	32	4597	144

 PH-7032 compound (S)-(+)-enantiomer	12	830	69
 PH-7032 compound racemate	15	396	26.4
 PH-7032 compound (S)-(+)-enantiomer	7	231	33
 PH-7032 compound racemate	25.5	1607	63
 PH-7032 compound (S)-(+)-enantiomer	12.5	459	36.7

(Molino Declaration ¶ 7).

The above results demonstrate that compounds **1** and **2** are more selective for DAT (DAT/NET ratio < 1) in the case of dichlofensine (**1**) and non-selective for NET, DAT,

or SERT in the case of the metabolite of dichlofensine (2) (Molino Declaration ¶ 8). In contrast, the above data shows that the PH-7032 compounds of the present application have a DAT/NET selectivity ≥ 5.1 which is selective for NET relative to DAT and has a SERT/NET selectivity ≥ 26.4 which is selective to NET relative to SERT (Id.). Thus, the compounds of the present invention are selective for NET relative to DAT and selective for NET relative to SERT (Id.).

Compounds that are selective for NET over transporters for other neurochemicals (e.g., DAT and SERT) have more beneficial therapeutic index than other compounds (Molino Declaration ¶9). By being more selective for NET over DAT and SERT (i.e. having a DAT/NET ratio of at least about 2:1 and a SERT/NET ratio of at least about 20:1), as shown above in Tables 1 and 2, the compounds of the present application possess fewer side effects than compounds **1** and **2** (Id.).

In the treatment of ADHD, drugs like methylphenidate (Ritalin®) possess a high selectivity for the dopamine transporter (DAT) over norepinephrine transporter (NET) (Molino Declaration ¶10). The DAT/NET selectivity ratio is 0.1 (Id.). Methylphenidate is a schedule II controlled substance, because it possesses the potential for addiction, which is also true for other drugs that affect the dopamine transporter (e.g., cocaine) (Id.). Compounds in this patent, which are more selective for NET rather than DAT, do not affect dopamine levels to the extent that methylphenidate does and should be much less likely to have this liability (Id.).

Known drugs that are selective Serotonin Reuptake Inhibitors ("SSRI")(e.g., Prozac™) are effective agents for the treatment of depression (Molino Declaration ¶11). No drugs in this class are currently prescribed for ADHD (Id.). This class of compounds is associated with certain side effects (e.g., sexual dysfunction) which is attributable to SERT selective nature of these compounds relative to NET (Id.). Compounds with the above DAT/NET and SERT/NET ratios do not possess the side effects of the SSRI class of drugs (Id.).

Since dichlofensine and the above-described metabolite of dichlofensine do not meet these claimed selectivity ratios, neither Tirelli, Salama, nor the Swiss and German Applications (to the extent directed to these compounds) can anticipate the claims of the present application.

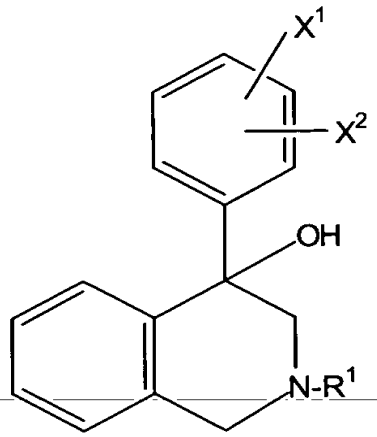
Although the Swiss and German Applications disclose other compounds besides dichlofensine and the above-described metabolite of dichlofensine, there is no evidence that such compounds have the claimed DAT/NET selectivity and SERT/NET selectivity ratios. In any event, it is well established that a reference describing a large class of compounds and having relatively few of those compounds encompassed by the claims of an application do not anticipate those claims. See In re Ruschig, 343 F.2d 965, 145 USPQ 274 (CCPA 1965). This is especially true where the reference demonstrates a preference for compounds other than those claimed. In the Swiss and German Applications, the specifically disclosed compounds involve substitution of the pendant aryl ring with 3-chloro, 4-chloro, or 3,4-dichlorophenyl, while the 6-position and 7-position substituents are 6-methoxy, 7-methoxy, or 6,7-dimethoxyphenyl. Thus, rather than provide guideposts to selected compounds encompassed by the claims, these references, in fact, emphasize compounds (e.g., dichlofensine and a metabolite thereof) which are clearly outside the scope of the claims.

For all of these reasons, the rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 102(b) should be withdrawn.

The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 103 for obviousness over the German Application or Japanese Patent Application Serial No. 4193867 to Nippon Shinyaku Co. Ltd. ("Japanese Application") is respectfully traversed.

The German Application is described above, and the Molino Declaration demonstrated that dichlofensine and the above-described metabolite of dichlofensine, which are preferred by the German Application do not meet the claimed selectivity values.

The Japanese Application describes compounds of the following formula:



(I)

X^1 and X^2 are hydrogen or a halogen and

R^1 is a 1 to 3 carbon alkyl group

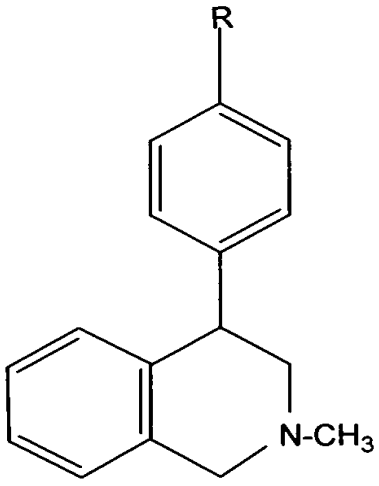
as well as pharmocologically permissible salts. Various compounds in accordance with this disclosure are set forth in the examples of the Japanese Application. By providing no evidence that such compounds have the claimed DAT/NET selectivity and SERT/NET selectivity ratios and offering no guideposts for selecting compounds with such ratios, it is submitted that the Japanese Application provides no suggestion of the claimed invention. Further, the claims of the present application require that R^3 and R^4 cannot both be H and that R^8 be H or halogen. Accordingly, the compounds of the Japanese Application are outside the scope of the claims.

It has been discovered that compounds that are selective for NET over transporters for other neurochemicals (e.g., DAT and SERT) have more beneficial therapeutic index that other compounds (Molino Declaration ¶ 9). By being more selective for NET over DAT and SERT (i.e. having a DAT/NET ratio of at least about 2:1 and a SERT/NET ratio of at least about 20:1), as shown above in Tables 1 and 2, the compounds of the present application possess fewer side effects than compounds **1** and **2** (Id.). In view of these unexpected advantages of the claimed invention, it is submitted that neither the German Application, nor the Japanese Application can render the claimed invention obvious. Therefore, the rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 103 should be withdrawn.

The rejection of claims 30 and 33-34 under 35 U.S.C. § 103 for obviousness over Trepanier, et. al., "3,4-Dihydroisocarostyril and 1,2,3,4-Tetrahydroisoquinoline Derivatives of Ephedrine," J. Med. Chem. 16(4): 342-47 (1973)("Trepanier"), Canadian Patent Application Serial No. 2,015,114 to Mondeshka, et. al., ("Mondeshka"), or Miller, et. al., "An Efficient Synthesis of 4-Aryl-1,2,3,4-Tetrahydorisoquinolines," Syn. Commun. 24(8): 1187-93 (1994) is respectfully traversed.

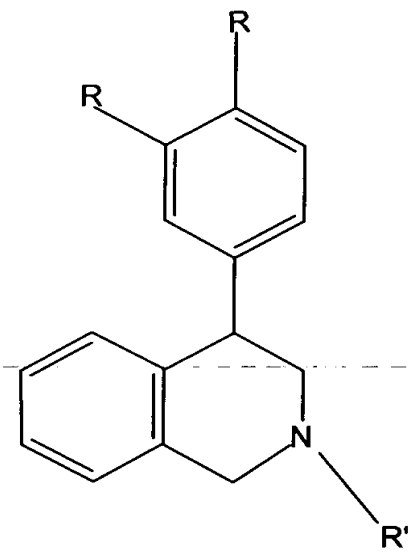
Trepanier discloses 3,4-dihydroisocarbostyril and 1,2,3,4-tetrahydroisoquinoline derivatives of ephedrine. Since the claims of the present application do not permit R^7 to be alkyl, Trepanier, which has a methyl in this position, fails to teach the claimed invention.

Mondeshka discloses



Since R^3 and R^4 cannot both be H in the claimed invention, Mondeshka clearly does not suggest what applicants have claimed.

Miller discloses 4-aryl substituted 1,2,3,4-tetrahydrosioquinolines of the formula:



1: R = OH, R' = H

2: R = H, R' = CH_3

Since R^3 and R^4 cannot both be H in the claimed invention, Miller clearly does not suggest what applicants have claimed.

Neither Trepanier, Mondeshka, nor Miller suggest the claimed compound with regard to structure, a DAT/NET ratio of at least about 2:1, or SERT/NET ratio of at least about 20:1. Since these references fail to suggest these limitations of the claims, the obviousness rejection based on them should be withdrawn.

The rejection of claims 30 and 33-34 under 35 U.S.C. § 103 for obviousness over Tirelli is respectfully traversed for the reasons noted above. This reference does not suggest the claimed DAT/NET ratio of at least about 2:1 and SERT/NET ratio of at least about 20:1. Tirelli also fails to disclose that compounds satisfying this limitation have unexpectedly fewer side effects. As a result, the obviousness rejection based on Tirelli should be withdrawn.

The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 112 (2^{nd} para.) for indefiniteness is respectfully traversed in view of the above amendments and the following remarks.

As to the description of formulae 1C and 1D in claim 1, it should be noted that the substituents of formula 1C are set forth on page 64, lines 12 to 13 (starting with what comes after "formula 1C") and the substituents of formula 1D are set forth on page 64, lines 14-15 (starting with what comes after "formula 1D"). See also page 64, lines 16-22.

Accordingly, the rejection under 35 U.S.C. § 112 (2nd para.) should be withdrawn.

The rejection of claims 1-36, 43-47, and 49 under 35 U.S.C. § 112 (1st para.) is respectfully traversed in view of the above amendments.

As to the request for information concerning the Information Disclosure Statement, the Bungard, Geene, and McComie references are books which cannot properly be copied and submitted to the U.S. Patent and Trademark Office. A copy of EP 599,338 has been provided in the accompanying Supplemental Information Disclosure Statement Under 37 CFR §§ 1.97-1.98. Finally, the entry for Cliffe, "(S)-N-tert Butyl-3-(4-(2-methoxyphenyl)-piperazin-1-yl)-2-phenylpropanamide[S]-WAY-100135): A Selective Antagonist at Presynaptic and Postsynaptic-5HT Receptors" J. Med. Chem. 36:1509-10 (1988) on the previously submitted PTO-1449 was not initialed in the copy of that form which was returned with the outstanding office action. It is respectfully requested that this reference (copy enclosed) be considered and the enclosed PTO-1449 form be initiated to reflect such consideration.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

Date: November 5, 2002

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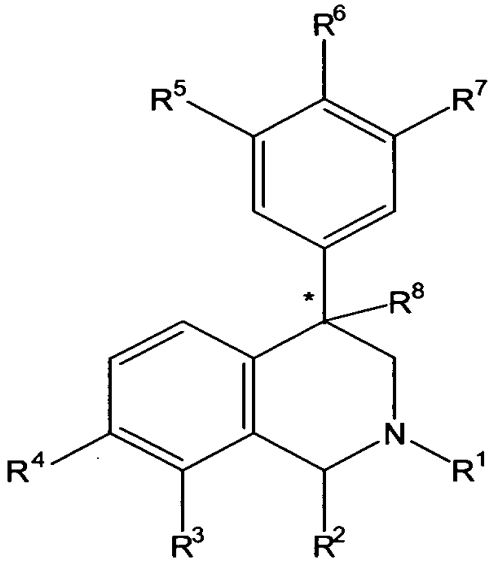
Date 11/5/02 Wendy L. Barry

APPENDIX
Version With Markings to Show Changes Made

In reference to the amendments, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

Please amend claims 1, 14, 23-24, and 30-32 as follows:

1. (Amended) A compound of the formula [IA-IF] I(A-F) having the following structure:



IA-IF

wherein:

the carbon atom designated * is in the R or S configuration;

R^1 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted with 1 to 3 substituents independently selected at each occurrence thereof from C_1-C_3 alkyl, halogen, aryl, -CN, OR^9 and $-NR^9R^{10}$;

R^2 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl or C_1-C_6 haloalkyl;

R^3 is H, halogen, $-OR^{11}$, $-S(O)_nR^{12}$, $-S(O)_nNR^{11}R^{12}$, -CN, $-C(O)R^{12}$, $-C(O)NR^{11}R^{12}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7

cycloalkylalkyl, -O(phenyl) or -O(benzyl), wherein each of -O(phenyl) and -O(benzyl) is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy, or wherein R^3 is a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7 cycloalkylalkyl group, then said group is optionally substituted with from 1 to 3 substituents selected independently at each occurrence thereof from C_1-C_3 alkyl, halogen, aryl, -CN, -OR^9 and -NR^9R^{10}; provided that for compounds of formula IA, R^3 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted with from 1 to 3 substituents selected independently at each occurrence thereof from C_1-C_3 alkyl, halogen, aryl, -CN, -OR^9 and -NR^9R^{10};

provided that for compounds of formula IB, R^3 is -O(phenyl), -O(benzyl), -$OC(O)R^{13}$ or $S(O)_nR^{12}$, each of -O(phenyl) and -O(benzyl) is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^4 is H, halogen, -OR^{11}, -$S(O)_nR^{12}$, -$S(O)NR^{11}R^{12}$, -CN, -$C(O)R^{12}$, -$C(O)NR^{11}R^{12}$, -$NR^{11}R^{12}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, -O(phenyl) or -O(benzyl), wherein each of -O(phenyl) and -O(benzyl) is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 halolkyl, or C_1-C_4 alkoxy and wherein R^4 is a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7 cycloalkylalkyl group, then said group is optionally substituted with from 1 to 3 substituents selected independently at each occurrence thereof from C_1-C_3 alkyl, halogen, aryl, -CN, -OR^9 and -NR^9R^{10}; provided that for compounds of formula IC, R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7 cycloalkylalkyl, each of which is optionally substituted; provided that for compounds of formula ID, R^4 is -O(phenyl), -O(benzyl), -$OC(O)R^{13}$, -$NR^{11}R^{12}$ or -$S(O)_nR^{12}$, each of -O(phenyl) and -O(benzyl) being optionally substituted, wherein R^3 and R^4 are not both H;

R^5, R^6 and R^7 in compounds of each of the formulae IA, IB, IC, ID, IE and IF are each independently H, halogen, -OR^{11}, -$S(O)_nR^{12}$, -CN, -$C(O)R^{12}$, -$NR^{11}R^{12}$, -$C(O)NR^{11}R^{12}$, -$NR^{11}C(O)R^{12}$, -$NR^{11}C(O)_2R^{12}$, -$NR^{11}C(O)NR^{12}R^{13}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7 cycloalkylalkyl, wherein each of R^5, R^6 and R^7 is a C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_4-C_7

cycloalkylalkyl group, then said group is optionally substituted with from 1 to 3 substituents selected independently at each occurrence thereof from C_1-C_3 alkyl, halogen, aryl, -CN, -OR^9 and -NR^9R^{10}, or R^5 and R^6 or R^6 and R^7 may be -O-$C(R^{12})_2$-O-; provided that for compounds of formula IE at least one of R^5 or R^7 is fluoro, chloro, or methyl; or R^5 or R^6 are each independently -O-$C(R^{12})_2$-O- in compounds of the formulae IE, but only where R^7 is fluoro, chloro or methyl; or R^7 and R^6 can independently also be -O-$C(R^{12})_2$-O- in compounds of the formulae IE, but only where R^5 is fluoro, chloro or methyl;

R^8 is H[,] or halogen [, or OR^{11}], provided that for compounds of formula IF, R^8 is halogen;

R^9 and R^{10} are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, -$C(O)R^{13}$, phenyl or benzyl, where phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy; or R^9 and R^{10} are taken together with the nitrogen to which they are attached to form piperideine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, or thiomorpholine;

R^{11} is H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, -$C(O)R^{13}$, phenyl or benzyl, where R^{11} is a C_1-C_4 alkyl, phenyl or benzyl group, then said group is optionally substituted from 1 to 3 times with a substituent selected independently at each occurrence thereof from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, or C_1-C_4 alkoxy;

R^{12} is H, amino, C_1-C_4 alkyl, (C_1-C_4 alkyl)amino, C_1-C_4 haloalkyl, C_1-C_4 alkoxyalkyl, C_3-C_6 cycloalkyl, C_4-C_7 cycloalkylalkyl, phenyl or benzyl, where phenyl or benzyl is optionally substituted from 1 to 3 times with a substituent selected independently from halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy; or R^{11} and R^{12} are taken together with the nitrogen to which they are attached to form piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, or thiomorpholine;

provided that only one of R^9 and R^{10} or R^9 and R^{10} are taken together with the nitrogen to which they are attached to form piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, or thiomorpholine;

R^{13} is C_1-C_4 alkyl, C_1-C_4 haloalkyl or phenyl;

n is 0, 1, or 2, and;

aryl is phenyl which is optionally substituted 1-3 times with halogen, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 alkoxy, or

an oxide thereof, or a pharmaceutically acceptable salt thereof, [a solvate thereof, or a prodrug thereof] wherein the compound has a binding affinity for dopamine transporter protein to a binding affinity for norepinephrine transporter protein ratio of at least 2:1 and a binding affinity for serotonin transporter protein to a binding affinity for norepinephrine transporter protein ratio of at least 20:1.

14. (Amended) The compound of claim 1, wherein [R^3 and R^4 are each H or wherein] R^3 and R^4 are each halogen.

30. (Amended) A compound according to claim 1, selected from the group consisting of the following compounds:

2,7-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
4-(4-methoxy)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;
2,7-dimethyl-4-(4-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline;
2,7-dimethyl-4-(3-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline;
4-(3,4-difluoro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;
2,7-dimethyl-4-(4-fluoro-3-methyl)phenyl-1,2,3,4-tetrahydroisoquinoline;
4-(3-chloro-4-fluoro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;
4-(3-chloro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;
2,7-dimethyl-4-(4-methyl)phenyl-1,2,3,4-tetrahydroisoquinoline;
2,7-dimethyl-4-(3-fluoro-4-methyl)phenyl-1,2,3,4-tetrahydroisoquinoline;
4-(4-chloro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;
4-(4-chloro-3-fluoro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;
4-(3,4-dichloro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;
7-ethyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;
4-(3,4-difluoro)phenyl-7-ethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;
7-fluoro-4-(4-methoxy)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;
7-fluoro-4-(3-fluoro-4-methoxy)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;
7-fluoro-4-(3-fluoro-4-methyl)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;
7-fluoro-4-(4-chloro-3-fluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

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4-(3,4-difluoro)phenyl-7-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro)phenyl-7-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline;

7-cyano-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

2-methyl-4-phenyl-7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;

4-phenyl-1,2,7-trimethyl-1,2,3,4-tetrahydroisoquinoline;

[4-(4-chloro)phenyl-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline;

4-(3,4-difluoro)phenyl-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline;]

4-phenyl-2,7,8-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;

2,7-dimethyl-8-fluoro-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

2,8-dimethyl-7-fluoro-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

2,7-dimethyl-8-methoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

2,7-dimethyl-8-hydroxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

2-methyl-4-phenyl-7-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;

4-(3,4-difluoro)phenyl-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-fluoro-3-methyl)phenyl-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-fluoro-4-methyl)phenyl-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

7-methoxy-4-(3-methyl)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

2-methyl-7-phenoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

7-(4-methoxy)phenoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

7-benzyloxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

7-hydroxy-2-methyl-4-(3-methyl)phenyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-fluoro-4-methyl)phenyl-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-fluoro-3-methyl)phenyl-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3,4-difluoro)phenyl-7-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

[4-(3-cyano)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;]

2,8-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

2,8-dimethyl-4-(4-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline;

4-(3,4-difluoro)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

4-(3,5-difluoro)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

2,8-dimethyl-4-(3-fluoro)phenyl-1,2,3,4-tetrahydroisoquinoline;

2,8-dimethyl-4-(4-fluoro-3-methyl)phenyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro-4-fluoro)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

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4-(3,4-dichloro)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-chloro)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-chloro-3-fluoro)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

2,8-dimethyl-4-(4-methoxy)phenyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-cyano)phenyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline;

2,8-dimethyl-4-(4-trifluoromethyl)phenyl-1,2,3,4-tetrahydroisoquinoline;

2,8-dimethyl-4-(4-methyl)phenyl-1,2,3,4-tetrahydroisoquinoline;

2-methyl-8-(N-methylamino)methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

8-(hydroxy)methyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

2-methyl-4-phenyl-8-sulfonamide-1,2,3,4-tetrahydroisoquinoline;

2-methyl-8-(N-methyl)sulfonamide-4-phenyl-1,2,3,4-tetrahydroisoquinoline;

8-methoxy-2-methyl-4-(4-methyl)phenyl-1,2,3,4-tetrahydroisoquinoline;

4-(3,5-difluoro)phenyl-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro)phenyl-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3,4-dichloro)phenyl-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-chloro-3-fluoro)phenyl-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro-4-fluoro)phenyl-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline;

[4-(3,5-difluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro-5-fluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;]

4-(3,5-difluoro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro-5-fluoro)phenyl-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline;

[2-methyl-4-(3,4,5-trifluoro)phenyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-fluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-fluoro-4-methyl)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-fluoro-3-methyl)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3,4-difluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-chloro-3-fluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-chloro-4-fluoro)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(3-cyano)phenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-acetanilide)-2-methyl-1,2,3,4-tetrahydroisoquinoline;

4-(4-chloro)phenyl-4-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline;

(3,5-difluoro)-4-phenyl-1,2,7-trimethyl-1,2,3,4-tetrahydroisoquinoline;]

4-(3,5-difluorophenyl-1,2,7-trimethyl-1,2,3,4-tetrahydroisoquinoline;

(8-fluoro-2-methyl-4-phenyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-N-methylmethanamine;

[(2-methyl-4-phenyl-7-isoquinolinyl)-N-methylmethanamine;]

2-methyl-4-phenyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-N-methylmethanamine;

[N-methyl(2-methyl-4-phenyl-7-isoquinolinyl)-N-methylmethanamine;]

N-methyl(2-methyl-4-phenyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-N-methylmethanamine;

8-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydro-7-isoquinolinecarbonitrile; and

(2-methyl-4-phenyl-1,2,3,4-tetrahydro-7-isoquinolinyl)methanol; and

[2-ethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline; and]

an oxide thereof, or a pharmaceutically acceptable salt thereof[, a solvate thereof, or prodrug thereof].

31. (Amended) A compound according to claim 1, selected from [table C] the group consisting of the following compounds:

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
1.	Me	H	H	Me	H	H	H	H
2.	Me	H	H	Me	H	OMe	H	H
3.	Me	H	H	Me	H	F	H	H
4.	Me	H	H	Me	F	H	H	H
5.	Me	H	H	Me	F	F	H	H
6.	Me	H	H	Me	Me	F	H	H
7.	Me	H	H	Me	Cl	F	H	H
8.	Me	H	H	Me	Cl	H	H	H
9.	Me	H	H	Me	H	Me	H	H
10.	Me	H	H	Me	F	Me	H	H
11.	Me	H	H	Me	H	Cl	H	H
12.	Me	H	H	Me	F	Cl	H	H
13.	Me	H	H	Me	Cl	Cl	H	H
14.	Me	H	H	Et	H	H	H	H
15.	Me	H	H	Et	F	F	H	H
16.	Me	H	H	F	H	OMe	H	H
17.	Me	H	H	F	F	OMe	H	H
18.	Me	H	H	F	F	Me	H	H
19.	Me	H	H	F	F	Cl	H	H
20.	Me	H	H	F	F	F	H	H
21.	Me	H	H	F	Cl	H	H	H

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	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
22.	Me	H	H	CN	H	H	H	H
23.	Me	H	H	CF_3	H	H	H	H
24.	Me	Me	H	Me	H	H	H	H
25.	Me	H	Me	Me	H	H	H	H
26.	Me	H	F	Me	H	H	H	H
27.	Me	H	Me	F	H	H	H	H
28.	Me	H	OMe	Me	H	H	H	H
29.	Me	H	OH	Me	H	H	H	H
30.	Me	H	H	OCF_3	H	H	H	H
31.	Me	H	H	OMe	F	F	H	H
32.	Me	H	H	OMe	Me	F	H	H
33.	Me	H	H	OMe	F	Me	H	H
34.	Me	H	H	OMe	Me	H	H	H
35.	Me	H	H	O(Ph)	H	H	H	H
36.	Me	H	H	O(4-OmePh)	H	H	H	H
37.	Me	H	H	$O(CH_2Ph)$	H	H	H	H
38.	Me	H	H	OH	Me	H	H	H
39.	Me	H	H	OH	F	Me	H	H
40.	Me	H	H	OH	Me	F	H	H
41.	Me	H	H	OH	F	F	H	H
42.	Me	H	Me	H	H	H	H	H
43.	Me	H	Me	H	H	F	H	H
44.	Me	H	Me	H	F	F	H	H
45.	Me	H	Me	H	F	H	F	H
46.	Me	H	Me	H	F	H	H	H
47.	Me	H	Me	H	Me	F	H	H
48.	Me	H	Me	H	Cl	F	H	H
49.	Me	H	Me	H	Cl	Cl	H	H
50.	Me	H	Me	H	Cl	H	H	H
51.	Me	H	Me	H	H	Cl	H	H
52.	Me	H	Me	H	F	Cl	H	H
53.	Me	H	Me	H	H	OMe	H	H
54.	Me	H	Me	H	H	CN	H	H
55.	Me	H	Me	H	H	CF_3	H	H
56.	Me	H	Me	H	H	Me	H	H
57.	Me	H	CH_2NHMe	H	H	H	H	H
58.	Me	H	CH_2OH	H	H	H	H	H
59.	Me	H	SO_2NH_2	H	H	H	H	H
60.	Me	H	SO_2NHMe	H	H	H	H	H
61.	Me	H	OMe	H	H	Me	H	H
62.	Me	H	OMe	H	F	H	F	H
63.	Me	H	OMe	H	Cl	H	H	H
64.	Me	H	OMe	H	Cl	Cl	H	H
65.	Me	H	OMe	H	F	Cl	H	H
66.	Me	H	OMe	H	Cl	F	H	H
67.	Me	H	H	Me	F	H	F	H
68.	Me	H	H	Me	F	H	Cl	H

APPENDIX
Version With Markings to Show Changes Made

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
69.	Me	Me	H	Me	F	H	F	H
70.	Me	H	H	Me	F	F	F	H
71.	Et	H	H	Me	H	F	H	H
72.	Me	H	F	CH_2Me	H	H	H	H
73.	Me	H	H	CH_2NH_2	H	H	H	H
74.	Me	H	H	CH_2NHMe	H	H	H	H
75.	Me	H	OH	CN	H	H	H	H
76.	Me	H	H	CH_2OH	H	H	H	H

32. (Amended) A compound according to claim 1, wherein the enantiomer is selected from [table D] the group consisting of the following compounds:

	R^1	R^2	R^3	R^4
1.	H	H	Me	F
2.	OMe	H	F	F
3.	Me	H	F	F
4.	H	H	Cl	F
5.	H	H	F	F
6.	Me	F	H	F
7.	Me	H	F	H
8.	Me	H	H	F